HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XULANE® safely and effectively. See full prescribing information for XULANE.

XULANE® (norelgestromin and ethinyl estradiol transdermal system)
Initial U.S. Approval: 2001

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL

See full prescribing information for complete boxed warning.

Women over 35 years old who smoke should not use Xulane. (4)
Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptives (CHC) use. (4)
There may be an increased risk of venous thromboembolism (VTE) among women who use the Xulane patch compared to women who use certain oral contraceptives. (5.1)
The pharmacokinetic (PK) profile of ethinyl estradiol (EE) for the norelgestromin and ethinyl estradiol transdermal system is different from the PK profile for oral contraceptives in that it has higher area under the time-concentration curve, steady state concentrations and lower peak concentrations. (5.2)

RECENT MAJOR CHANGES

Contraindications (4) 4/2017
Warnings (5.4) 4/2017

INDICATIONS AND USAGE

Xulane is a progesterin/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch. (1)
Limitation of Use: Xulane may be less effective in preventing pregnancy in women at or above 198 lbs (90 kg). (1)

DOSE AND ADMINISTRATION

- Xulane uses a 28-day (4-week) cycle. Apply a new patch to the upper outer arm, abdomen, buttock or back each week for 3 weeks (21 total days). Week 4 is patch-free. (2.1, 2.3)
- Apply each new patch on the same day of the week. Wear only one patch at a time. (2.1)
- Do not cut or alter the patch in any way. (2.1)

DOSE FORMS AND STRENGTHS

Transdermal system: 150 mcg/day norelgestromin and 35 mcg/day ethinyl estradiol. (3)

ADVERSE REACTIONS

The most frequent adverse reactions reported during clinical trials (≥ 5%) were breast symptoms, nausea/vomiting, headache, application site disorder, abdominal pain, dysmenorrhea, vaginal bleeding and menstrual disorders, and mood, affect and anxiety disorders. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of CHCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with CHCs. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2017
NEETS:R14/PL:NEETS:R13

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL

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WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL

Cigarette Smoking and Serious Cardiovascular Risks

Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including Xulane, should not be used by women who are over 35 years of age and smoke.

RISK OF VENOUS THROMBOEMBOLISM

The risk of venous thromboembolism (VTE) among women aged 15 to 44 who used the norelgestromin and ethinyl estradiol transdermal system compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2, and all studies found a statistically significant increase of VTE risk with current users of norelgestromin and ethinyl estradiol transdermal system (see Warnings and Precautions (5.1)).

Pharmacokinetic (PK) Profile of Ethinyl Estradiol (EE)

The PK profile for the norelgestromin and ethinyl estradiol transdermal system is different from the PK profile for oral contraceptives in that it has a higher steady state concentrations and a lower peak concentration. Area under the time-concentration curve (AUC) and average concentration at steady state (C₀INF) for EE are approximately 60% higher in women using norelgestromin and ethinyl estradiol transdermal system compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, the peak concentration (C₀max) for EE is approximately 25% lower in women using norelgestromin and ethinyl estradiol transdermal system. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using norelgestromin and ethinyl estradiol transdermal system compared with women using oral contraceptives containing 30 mcg to 35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including VTE (see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)).

1 INDICATIONS AND USAGE

Xulane is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

Limitation of Use:

- Xulane may be less effective in preventing pregnancy in women who weigh 198 lbs (90 kg) or more.

2 DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Xulane must be used exactly as directed. Complete instructions to facilitate patient counseling on proper system usage may be found in the FDA-Approved Patient Labeling.

2.1 How to Use Xulane

The Xulane transdermal system uses a 28-day (4-week) cycle. A new patch is applied each week for 3 weeks (21 total days). Week 4 is patch-free. Withdrawal bleeding is expected during this time.

Every new patch should be applied on the same day of the week. This day is known as the “Patch Change Day.” For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time.

Do not cut, damage or alter the Xulane patch in any way. If the Xulane patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.

On the day after Week 4 ends, a new 4-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.

2.2 How to Start Using Xulane

The woman has two options for starting the patch and she should choose the option that is right for her:

- **First Day Start**—The woman should apply her first patch during the first 24 hours of her menstrual period.
- **Sunday Start**—The woman should apply her first patch on the first Sunday after her menstrual period begins. With this option, a non-hormonal backup method of birth control, such as a condom and spermicide or diaphragm and spermicide, is needed for the first 7 days of the first cycle only. If her period starts on a Sunday, the first patch should be applied that day, and no backup contraception is needed.
- **When Switching From the Pill or Vaginal Contraceptive Ring to the Patch**—If the woman is switching from the pill or vaginal contraceptive ring to Xulane, she should complete her current pill cycle or vaginal ring cycle and apply the first Xulane patch on the day she would normally start her next pill or insert her next vaginal ring. If she does not get her period within a week after taking the last active pill or removing the last vaginal ring, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start Xulane for contraception. If the patch is applied more than a week after taking the last active pill or removal of the last vaginal ring, she should use a non-hormonal contraceptive concurrently for the first 7 days of patch use.

Use after Childbirth

Start contraceptive therapy with Xulane in women who elect not to breastfeed no sooner than 4 weeks after childbirth due to increased risk of thromboembolism. If a woman begins using Xulane postpartum, and has not yet had a period, consider the possibility of ovulation and conception occurring prior to use of Xulane, and instruct her to use an additional method of contraception, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days. (See Warnings and Precautions (5.1) and Pregnancy (8.1).)

Use after Abortion or Miscarriage

After an abortion or miscarriage that occurs in the first trimester, Xulane may be started immediately. An additional method of contraception is not needed if Xulane is started immediately. If use of Xulane is not started within 5 days following a first trimester abortion, the woman should follow the instructions for a woman starting Xulane for the first time. In the meantime she should be advised to use a non-hormonal contraceptive method. Ovulation may occur within 10 days of an abortion or miscarriage.

Start Xulane no earlier than 4 weeks after a second trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. (See Contraindications (4) and Warnings and Precautions (5.1).)

2.3 How to Apply Xulane

CHOOiNING A PLACE ON THE BODY TO PUT THE PATCH

- The patch may be placed on the upper outer arm, abdomen, buttock or back in a place where it won’t be rubbed by tight clothing. For example, it should not be placed under the waistband of clothing.
- The patch should not be placed on the breasts, on cut or irritated skin, or on the same location as the previous patch.

Before applying the patch:

- The woman should make sure the skin is clean and dry.
- She should not use lotions, creams, oils, powders, or make-up at the patch site. It may cause the patch to fail to stick properly or to become loose.

HOW TO APPLY THE PATCH

1. The woman should tear open the pouch at the top edge and one side edge. She should peel open the foil pouch. She should gently remove the contents of the foil pouch and discard the additional pieces of film above and below the patch.

2. The woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.

3. The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.

4. The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin.

5. She should run her fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the patch.

6. The woman should check her patch every day to make sure all edges are sticking correctly.

7. **When to Change the Xulane Patch**

- The patch works for 7 days (1 week). The woman should apply a new patch on the same day each week (her Patch Change Day) for 3 weeks in a row. She must make sure she has removed her old patch prior to applying the new patch.
- During Week 4, she DOES NOT wear a patch. She must make sure she removes her old patch. (Her period should begin during this week.)
• Following Week 4, she repeats the cycle of three weekly applications followed by a patch-free week.

WHAT IF THE PATCH BECOMES LOOSE OR FALLS OFF?
The patch must stick securely to the skin to work properly. If the Xulane patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs. The woman should not reapply the patch, because if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it.

If a patch edge lifts up:
• The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. She should run her fingers over the entire surface area to smooth out any “wrinkles” around the edges of the patch.
• If her patch does not stick completely, she should remove it and apply a replacement patch.
• She should not tape or wrap the patch to her skin or reapply a patch that is partially adhered to clothing.

If the patch has been off or partially off:
• For less than 1 Day, she should try to reapply it. If the patch does not adhere completely, she should apply a new patch immediately. (No backup contraception is needed and her Patch Change Day will stay the same.)
• For more than 1 Day or if she is not sure for how long, she may not be protected from pregnancy. To reduce this risk, she should apply a new patch and start a new 4-week cycle. She will now have a new Patch Change Day and MUST USE NON-HORMONAL BACKUP CONTRACEPTION (such as a condom and spermicide or diaphragm and spermicide) for the first week of her new cycle.

IF THE WOMAN FORGETS TO CHANGE HER PATCH
• at the start of any patch cycle (Week 1/Day 1): SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should apply the first patch of her new cycle as soon as she remembers. There is now a new “Patch Change Day” and a new “Day 1.” The woman must use back-up contraception, such as a condom and spermicide or diaphragm and spermicide, for the first week of the new cycle.
• in the middle of the patch cycle (Week 2/Day 8 or Week 3/Day 15),
  – for 1 or 2 days (up to 48 hours), she should apply a new patch immediately. The next patch should be applied on the usual “Patch Change Day.” No back-up contraception is needed.
  – for more than 2 days (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new 4-week cycle immediately by putting on a new patch. There is now a new “Patch Change Day” and a new “Day 1.” The woman must use back-up contraception for 1 week.
• at the end of the patch cycle (Week 4/Day 22),
  – If the woman forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual “Patch Change Day,” which is the day after Day 28. No back-up contraception is needed.

Under no circumstances should there be more than a 7-day patch-free interval between cycles. If there are more than 7 patch-free days, THE WOMAN MAY NOT BE PROTECTED FROM PREGNANCY and back-up contraception, such as a condom and spermicide or diaphragm and spermicide, must be used for 7 days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended drug-free period. If she has had intercourse during such an extended patch-free interval, consider the possibility of pregnancy.

Change Day Adjustment
If the woman wishes to change her Patch Change Day, she should complete her current cycle, removing the third Xulane patch on the correct day. During the patch-free week, she may select an earlier Patch Change Day by applying a new Xulane patch on the desired day. In no case should there be more than 7 consecutive patch-free days.

Breakthrough Bleeding or Spotting
In the event of unscheduled or breakthrough bleeding or spotting (bleeding that occurs on the days that Xulane is worn), treatment should be continued. If unscheduled bleeding persists longer than a few cycles, consider causes other than Xulane.

If the woman does not have scheduled or withdrawal bleeding (bleeding that should occur during the patch-free week), she should resume treatment on the next scheduled Change Day. If Xulane has been used correctly, the absence of withdrawal bleeding is not necessarily an indication of pregnancy. Nevertheless, consider the possibility of pregnancy, especially if absence of withdrawal bleeding occurs in 2 consecutive cycles. Discontinue Xulane if pregnancy is confirmed.

In Case of Skin Irritation
If patch use results in uncomfortable irritation, the patch may be removed and a new patch may be applied to a different location until the next Change Day. Only one patch should be worn at a time.

Additional Instructions for Dosing
Unscheduled bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives. In case of breakthrough bleeding, as in all cases of irregular bleeding from the vagina, consider nonfunctional causes. In case of undiagnosed persistent or recurrent abnormal bleeding from the vagina, take adequate diagnostic measures to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another method of contraception may solve the problem.

Use of Hormonal Contraceptives in the Event of a Missed Menstrual Period
1. If the woman has not adhered to the prescribed schedule, consider the possibility of pregnancy at the time of the first missed period. Discontinue use of Xulane if pregnancy is confirmed.
2. If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches. However, if she has adhered to the prescribed regimen, misses one period and has symptoms associated with pregnancy, rule out pregnancy. Discontinue Xulane use if pregnancy is confirmed.
3. If the woman has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Xulane use if pregnancy is confirmed.

3 Doseage Forms and Strengths
Xulane® (norelgestromin and ethinyl estradiol transdermal system) is available in one strength of 150 mcg/day norelgestromin (NGMN) and 35 mcg/day ethinyl estradiol (EE). Xulane® is a 14 cm² peach, transdermal system printed with “Xulane® (norelgestromin and ethinyl estradiol) 150/35 mcg per day” in brown ink. Each system contains 4.86 mg norelgestromin, USP and 0.53 mg ethinyl estradiol, USP.

4 Contraindications
Do not prescribe Xulane to women who are known to have the following conditions:
• A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  o Smoke, if over age 35 [see Boxed Warning, and Warnings and Precautions (5.1)]
  o Have deep vein thrombosis or pulmonary embolism, now or in the past [see Warnings and Precautions (5.1)]
  o Have inherited or acquired hypercoagulopathies [see Warnings and Precautions (5.1)]
  o Have cerebrovascular disease [see Warnings and Precautions (5.1)]
  o Have coronary artery disease [see Warnings and Precautions (5.1)]
  o Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see Warnings and Precautions (5.1)]
  o Have uncontrolled hypertension [see Warnings and Precautions (5.1)]
  o Have diabetes mellitus with vascular disease [see Warnings and Precautions (5.7)]
  o Have headaches with focal neurological symptoms or have migraine headaches with aura
• Women over age 35 with any migraine headaches [see Warnings and Precautions (5.8)]
• Liver tumors, benign or malignant, or liver disease [see Warnings and Precautions (5.3), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]
• Undiagnosed abnormal uterine bleeding [see Warnings and Precautions (5.9)]
• Pregnancy, because there is no reason to use hormonal contraceptives during pregnancy [see Warnings and Precautions (5.10) and Use in Specific Populations(8.1)]
• Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [see Warnings and Precautions (5.11)]
• Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for alanine aminotransferase (ALT) elevations [see Warnings and Precautions (5.14)]

5 Warnings and Precautions
5.1 Thromboembolic Disorders and Other Vascular Problems
Stop Xulane if an arterial or deep venous thrombotic event (VTE) occurs.

Stop Xulane if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

If feasible, stop Xulane at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE. Discontinue use of Xulane during prolonged immobilization and resume treatment based on clinical judgment.

Start Xulane no earlier than 4 weeks after delivery, in women who are not breastfeeding. The next cycle should be started on the usual “Patch Change Day,” which is the day after Day 28. No back-up contraception is needed.

The five studies are:
1. The Boston Collaborative Drug Surveillance Program (BCDSP) with NGM-containing oral contraceptives as the comparator, including a 24-month extension, based on the Ingenuity Research Datasat; this study included patient chart review to confirm the VTE occurrence.
2. The 13 Ingenix study with NGM-containing oral contraceptives as the comparator, including a 24-month extension, based on the Ingenix Research Datasat; this study included patient chart review to confirm the VTE occurrence.
contraceptives as the comparator (BCDSP NGM), including two extensions of 17 and 14 months, respectively, based on the Pharmetrics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.

- BCDSP with LNG-containing oral contraceptives as the comparator, based on the Pharmetrics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.

- FDA-funded study with two groups of comparators: (1) LNG-containing oral contraceptives, and (2) oral contraceptives that contain LNG, norethindrone, and norgestimate, based on Kaiser Permanente and Medicaid databases. This study used all cases of VTE (idiopathic and non-idiopathic) and included patient chart review to confirm the VTE occurrence.

The i3 Ingenix and BCDSP NGM studies have provided data on additional cases identified in the original studies; however, each study extension was not powered to provide independent estimates of risk. The pooled estimates provide the most reliable estimates of VTE risk. Risk ratios from the original and various extensions of the i3 Ingenix and BCDSP NGM studies are provided in Table 1. The results of these studies are presented in Figure 1.

Table 1: Estimates (Risk Ratios) of Venous Thromboembolism Risk in Current Users of Norelgestromin and Ethinyl Estradiol Transdermal System Compared to Combined Oral Contraceptive Users

<table>
<thead>
<tr>
<th>Epidemiologic Study</th>
<th>Comparator Product</th>
<th>Risk Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i3 Ingenix NGM Study in Ingenix Research Databasem1,2,7</td>
<td>LNG/35 mcg EE</td>
<td>2.2 (1.2 – 4.0)</td>
</tr>
<tr>
<td>BCDSPNGM Study in Pharmetrics database2,5</td>
<td>LNG/35 mcg EE</td>
<td>1.2 (0.9 – 1.8)</td>
</tr>
<tr>
<td>BCDSP LNG Study in Pharmetrics database4</td>
<td>LNG/30 mcg EE</td>
<td>2.0 (0.9 – 4.1)</td>
</tr>
<tr>
<td>BCDSP LNG Study in Marketscan database4</td>
<td>LNG/30 mcg EE</td>
<td>1.3 (0.8 – 2.1)</td>
</tr>
<tr>
<td>FDA-funded study in Kaiser Permanente and Medicaid databases1,2,9</td>
<td>LNG/30 mcg EE</td>
<td>1.4 (0.9 – 2.0)</td>
</tr>
<tr>
<td>LNG/30 mcg EE</td>
<td>1.2 (0.8 – 1.9)</td>
<td></td>
</tr>
</tbody>
</table>

* New users – i.e., women with no prior exposure to the drug studied during a pre-specified time period – are considered to be the most informative population to study in pharmacoepidemiologic safety studies. All estimates took account of new-user status. The method and time period used to identify "new users" varied from study to study.

In Sample: LNG = levonorgestrel

In Sample: EE = ethinyl estradiol

Increased risk of VTE is statistically significant

Followed risk ratio from references 1 and 6 covering the initial 33-month study plus 24-month extension. (Initial 33 months of data: Risk Ratio (95% CI) = 2.2 (1.1 – 5.1). Separate estimate from the 24 months of data on new cases not included in the previous estimate. Risk Ratio (95% CI) = 1.4 (0.5 – 3.5). These risk ratios are based on idiopathic cases (those in women without other known risk factors for VTE). If all VTE cases are considered, the pooled risk ratio and 95% CI are 2.0 (1.2 – 3.3).

BCDSP = Boston Collaborative Drug Surveillance Program. The risk ratios are based on idiopathic cases.

Followed risk ratio from references 2, 3, and 5 covering the initial 36-month study plus 17-month and 14-month extensions. (Initial 36 months of data: Risk Ratio (95% CI) = 0.9 (0.5 – 1.6). Separate estimate from 17 months of data on new cases not included in the previous estimate: Risk Ratio (95% CI) = 1.1 (0.6 – 2.1). Separate estimate from 14 months of data on new cases not included in the previous estimates: Risk Ratio (95% CI) = 2.4 (1.2 – 5.0).

NGM = norgestimate

46 months of data.

63 months of data.

84 months of data in FDA-funded study.

Results for “All users,” i.e., initiation and continuing use of study combination hormonal contraception: “All progestins”2/35 mcg EE. Risk Ratio (95% CI) = 1.6 (1.2 – 2.1). LNG and LNG/30 mcg EE. Risk Ratio (95% CI) = 1.3 (1.0 – 1.6).

Includes the following progestins: levonorgestrel (LNG), norethindrone, and norgestimate (NGM).

BCDSP = Boston Collaborative Drug Surveillance Program

EE = ethinyl estradiol

An increased risk of thromboembolic and thrombotic disease associated with the use of combination hormonal contraceptives (CHCs) is well established. Although the absolute VTE rates are higher for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the postpartum period (see Figure 2). The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of CHCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to CHCs gradually disappears after CHC use is discontinued. Figure 2 shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs, for pregnant women, and for women in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use CHCs are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 2: Likelihood of Developing a VTE

Use of CHCs also increases the risk of arterial thromboses such as, cerebrovascular events (thrombotic and hemorrhagic strokes) and myocardial infarctions, especially in women with other risk factors for these events. In general, the risk is greatest among older (> 35 years of age), hypertensive women who also smoke. Use CHCs with caution in women with cardiovascular disease risk factors.

5.2 PK Profile of Ethinyl Estradiol

The PK profile for the norelgestromin and ethinyl estradiol transdermal system is different from the PK profile for oral contraceptives in that it has a higher C max and a lower C ss. AUC and clearance for EE are approximately 50% higher in women using norelgestromin and ethinyl estradiol transdermal system compared with women using an oral contraceptive containing EE 35 mcg. In contrast, the C max for EE is approximately 25% lower in women using norelgestromin and ethinyl estradiol transdermal system. Inter-subject variability results in increased exposure to EE in some women using either norelgestromin and ethinyl estradiol transdermal system or oral contraceptives. However, inter-subject variability in women using norelgestromin and ethinyl estradiol transdermal system is higher. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using norelgestromin and ethinyl estradiol transdermal system compared with women using oral contraceptives containing 30 mcg to 35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism. (See Boxed Warning and Clinical Pharmacology (12.3)).

5.3 Liver Disease

Impaired Liver Function

Do not use Xulane in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver (see Contraindications (4)). Discontinue Xulane if jaundice develops. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal and CHC causation has been excluded.

5.4 High Blood Pressure

Xulane is contraindicated in women with benign and malignant liver tumors (see Contraindications (4)). Hepatic adenomas are associated with CHC use. An estimate of the attributable risk of liver disease (due to CHC use) is 3.3 cases/100,000 CHC users. Rupture of hepatic adenomas may cause death through intraperitoneal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 5 years) CHC users. However, the risk of liver cancers in CHC users is less than one case per million users.

5.5 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains obitavir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as CHCs. Discontinue Xulane prior to starting therapy with the combination drug regimen obitavir/paritaprevir/ritonavir, with or without dasabuvir (see Contraindications (4)). Xulane can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.6 Blood Pressure

An increase in blood pressure has been reported in women taking hormonal contraceptives, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.7 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease. A past history of CHC-related disease 

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some past studies have suggested that CHCs might increase the incidence of breast cancer, although there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

5.13 Effect on Binding Globulins

The estrogen component of CHCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.14 Monitoring

A woman who is taking hormonal contraceptive should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.15 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.16 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while using Xulane.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of combination hormonal contraceptives, including Xulane, are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke (see Boxed Warning and Warnings and Precautions (5.1))
- Vascular events, including venous and arterial thromboembolic events (see Warnings and Precautions (5.1))
- Liver disease (see Warnings and Precautions (5.3))

Adverse reactions commonly reported by users of combination hormonal contraceptives are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

5.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The data described below reflect exposure to norelgestromin and ethinyl estradiol transdermal system in 3330 sexually active women (3322 of whom had safety data) who participated in three Phase 3 clinical trials designed to evaluate contraceptive efficacy and safety. These subjects received six or 13 cycles of contraception (norelgestromin and ethinyl estradiol transdermal system or an oral contraceptive comparator in 2 of the trials). The women ranged in age from 18 to 45 years and were predominantly white (91%).

The most common adverse reactions (≥ 5%) reported during clinical trials were breast symptoms (including breast discomfort, engorgement and pain), nausea and/or vomiting, headache and emotional lability. Adverse drug reactions reported by ≥ 2.5% of norelgestromin and ethinyl estradiol transdermal system-treated subjects in these trials are shown in Table 3.

5.1.10 Hormonal Contraceptive Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue Xulane use if pregnancy is confirmed.

Administration of CHCs should not be used for a test of pregnancy (see Use in Specific Populations (8.11)).

5.1.11 Depression

Carefully observe women with a history of depression and discontinue Xulane if depression recurs to a serious degree.

5.1.12 Carcinoma of Breasts and Cervix

Xulane is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive (see Contraindications (4)). There is substantial evidence that CHCs do not increase the incidence of breast cancer. Although some past studies have suggested that CHCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

5.7 Carbohydrate and Lipid Metabolic Effects

Careful monitoring of prediabetic and diabetic women who take Xulane. CHCs may decrease glucose tolerance in a dose-related fashion. In a 6-cycle clinical trial with norelgestromin and ethinyl estradiol transdermal system there were no clinically significant changes in fasting blood glucose from baseline to end of treatment. Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on hormonal contraceptives.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using hormonal contraceptives.

5.8 Headache

If a woman taking Xulane develops new headaches that are recurrent, persistent or severe, evaluate the cause and discontinue Xulane if indicated.

Consider discontinuation of Xulane in the case of increased frequency or severity of migraine during hormonal contraceptive use (which may be pruridural of a cerebrovascular event).

5.9 Bleeding Irregularities

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough) bleeding and spotting sometimes occur in women using norelgestromin and ethinyl estradiol transdermal system. Consider non-hormonal causes and take adequate diagnostic measures to rule out malignancy, other pathology, or pregnancy in the event of unscheduled bleeding, as in the case of any abnormal vaginal bleeding. If pathology and pregnancy have been excluded, time or a change to another contraceptive product may resolve the bleeding. In the clinical trials, most women started their scheduled (withdrawal) bleeding on the fourth day of the drug-free interval, and the median duration of withdrawal bleeding was 5 to 6 days. On average, 26% of women per cycle had 7 or more total days of bleeding and/or spotting (this includes both scheduled and unscheduled bleeding and/or spotting). Three clinical studies of the efficacy of norelgestromin and ethinyl estradiol transdermal system in preventing pregnancy assessed scheduled and unscheduled bleeding (see Clinical Studies (14)) in 3,330 women who completed 22,155 cycles of exposure. A total of 36 (1.1%) of the women discontinued norelgestromin and ethinyl estradiol transdermal system at least in part, due to bleeding or spotting. Table 2 summarizes the proportion of subjects who experienced unscheduled (breakthrough) bleeding/spotting by treatment cycle.

Table 2: Unscheduled (Breakthrough) Bleeding/Spotting (Subjects Evaluable for Efficacy)

<table>
<thead>
<tr>
<th>Treatment Cycle</th>
<th>Pooled data from 3 studies N = 3319</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>2994</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>2743</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>2695</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>2541</td>
</tr>
<tr>
<td>Cycle 5</td>
<td>2532</td>
</tr>
<tr>
<td>Cycle 6</td>
<td>2494</td>
</tr>
<tr>
<td>Cycle 7</td>
<td>698</td>
</tr>
<tr>
<td>Cycle 8</td>
<td>692</td>
</tr>
<tr>
<td>Cycle 9</td>
<td>654</td>
</tr>
<tr>
<td>Cycle 10</td>
<td>621</td>
</tr>
<tr>
<td>Cycle 11</td>
<td>631</td>
</tr>
<tr>
<td>Cycle 12</td>
<td>617</td>
</tr>
<tr>
<td>Cycle 13</td>
<td>611</td>
</tr>
</tbody>
</table>

*Percentage of subjects with breakthrough bleeding/spotting events.

Amenorrhea and D oligomenorrhea

In the event of amenorrhea, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one patch or started the patch on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Some women may experience amenorrhea or oligomenorrhea after discontinuation of hormonal contraceptive use, especially when such a condition was pre-existent.

5.10 Hormonal Contraceptive Use Before or During Early Pregnancy

The most common adverse reactions (≥ 2.5% of Norelgestromin and Ethinyl Estradiol Transdermal System-treated subjects in these trials are shown in Table 3.

Table 3: Adverse Drug Reactions Reported by ≥ 2.5% of Norelgestromin and Ethinyl Estradiol Transdermal System-treated Subjects in Three Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>System/Organ Class*</th>
<th>Norelgestromin and Ethinyl Estradiol Transdermal System (n = 3322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
</tr>
<tr>
<td>Breast symptoms§</td>
<td>22.4%</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>7.8%</td>
</tr>
<tr>
<td>Vaginal bleeding and menstrual disorders¹</td>
<td>6.4%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16.6%</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>8.1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.3%</td>
</tr>
<tr>
<td>Migraine</td>
<td>2.7%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Application site disorder†</td>
<td>17.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.6%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.
Table 3: Adverse Drug Reactions Reported by ≥ 2.5% of Norelgestromin and Ethinyl Estradiol Transdermal System-treated Subjects in Three Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>System/Organ Class*</th>
<th>Norelgestromin and Ethinyl Estradiol Transdermal System (n = 3322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>2.3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2.5%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Vaginal yeast infection†</td>
<td>3.3%</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

* MedDRA version 10.0
† Represents a bundle of similar terms

Additional adverse drug reactions that occurred in < 2.5% of norelgestromin and ethinyl estradiol transdermal system-treated subjects in the above clinical trials datasets are:

- Gastrointestinal disorders: Abdominal distension
- General disorders and administration site conditions: Fluid retention†, malaise
- Hepatobiliary disorders: Cholecystitis
- Investigations: Blood pressure increased, lipid disorders†
- Musculoskeletal and connective tissue disorders: Muscle spasms
- Psychiatric disorders: Insomnia, libido decreased, libido increased
- Reproductive system and breast disorders: Galactorrhea, genital discharge, premenstrual syndrome, uterine spasm, vaginal discharge, vulvalogyn dyspareunia
- Respiratory, thoracic and mediastinal disorders: Pulmonary embolism
- Skin and subcutaneous tissue disorders: Chloasma, dermatitis contact, erythema, skin irritation

6.2 Postmarketing Experience

The following adverse reactions (Table 4) have been identified during postapproval use of norelgestromin and ethinyl estradiol transdermal system. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 4: Alphabetical List of Adverse Drug Reactions Identified During Postmarketing Experience with Norelgestromin and Ethinyl Estradiol Transdermal System by System Organ Class*

<table>
<thead>
<tr>
<th>System/organ class</th>
<th>Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Myocardial infarction†</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Hyperglycemia, insulin resistance</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Contact lens intolerance or complication</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Colitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Blood cholesterol abnormal, cholelithiasis, cholestasis, hepatic lesion, jaundice, low density lipoprotein increased</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic reaction†, urticaria</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Increased appetite</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</td>
<td>Breast cancer†, cervix carcinoma, hepatic adenoma, hepatic neoplasm</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia, migraine with aura</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anger, emotional disorder, frustration, irritability</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Breast mass, cervical dysplasia, fibroadenoma of breast, menstrual disorder†, suppressed lactation, uterine leiomyoma</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, eczema, erythema multiforme, erythema nodosum, photosensitivity reaction, pruritus generalized, rash†, seborrheic dermatitis, skin reaction</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Arterial thrombosis†, cerebrovascular accident†, deep vein thrombosis†, hemorrhage intracranial†, hypertension, hypertensive crisis, pulmonary embolism†, thrombosis†</td>
</tr>
</tbody>
</table>

* MedDRA version 10.0
† Represents a bundle of similar terms

7 DRUG INTERACTIONS

Consult the labeling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Xulane is a transdermal system with a contact surface area of 14 cm². It contains 4.86 mg of Norelgestromin and Ethinyl Estradiol Transdermal System.

8 USE IN SPECIFIC POPULATIONS

8.7 Renal Impairment

No studies with Xulane have been conducted in women with renal impairment. Xulane should be used with caution in women with renal impairment due to the potential for reduced renal elimination of the active ingredients.

8.8 Women with Weight ≥ 198 lbs (90 kg)

Xulane may be less effective in preventing pregnancy in women who weigh 198 lbs (90 kg) or more.

8.11 Pregnancy

In case of suspected overdose, all Xulane patches should be removed and symptomatic treatment given.

11 DESCRIPTION

Xulane is a transdermal system with a contact surface area of 14 cm². It contains 4.86 mg of Norelgestromin and Ethinyl Estradiol Transdermal System.
norgestrel, USP (NGMN) and 0.53 mg ethinyl estradiol, USP (EE), and its delivery rate is approximately 150 mcg of NGMN and 35 mcg of EE per day based on a comparative analysis with intravenous (IV) data. Following a single application of norelgestromin and ethinyl estradiol transdermal system, both NGMN and EE reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. In one of the clinical studies, Css concentrations across all subjects ranged from 0.305 to 1.53 ng/mL for NGMN and from 23 to 137 pg/mL for EE.

The systemic delivery rate of NGMN and EE from norelgestromin and ethinyl estradiol transdermal system is approximately 150 mcg of NGMN and 35 mcg of EE per day based on a comparative analysis with intravenous (IV) data. Following a single application of norelgestromin and ethinyl estradiol transdermal system, both NGMN and EE reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. In one of the clinical studies, Css concentrations across all subjects ranged from 0.305 to 1.53 ng/mL for NGMN and from 23 to 137 pg/mL for EE.

Absorption of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent.

The mean (%CV) PK parameters for NGMN and EE following a single application of norelgestromin and ethinyl estradiol transdermal system are summarized in Table 5. In multiple dose studies, AUC₀₋₁₆₈ for NGMN and EE was found to increase over time (Table 5). In a three-cycle study, these PK parameters reached steady state conditions during Cycle 3 (Figures 3 and 4). Upon removal of the patch, serum levels of EE and NGMN reach very low or non-measurable levels within 3 days.

Table 5: Mean (%CV) PK Parameters of NGMN and EE Following Three Consecutive Cycles of Norelgestromin and Ethinyl Estradiol Transdermal System Wear on the Buttock

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameter</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGMN</td>
<td>C₀ (ng/mL)</td>
<td>0.70 (58.4)</td>
<td>1.07 (42.4)</td>
<td>1.12 (50.3)</td>
<td>0.70 (40.1)</td>
<td>1.12 (50.3)</td>
<td>1.12 (50.3)</td>
</tr>
<tr>
<td></td>
<td>AUC₀₋₁₆₈ (ng·h/mL)</td>
<td>107.0 (44.4)</td>
<td>105.0 (43.4)</td>
<td>136.0 (43.5)</td>
<td>120.0 (43.5)</td>
<td>120.0 (43.5)</td>
<td>120.0 (43.5)</td>
</tr>
<tr>
<td>EE</td>
<td>C₀ (pg/mL)</td>
<td>46.4 (38.5)</td>
<td>47.6 (40.4)</td>
<td>50.0 (42.5)</td>
<td>49.6 (54.4)</td>
<td>50.0 (42.5)</td>
<td>49.6 (54.4)</td>
</tr>
<tr>
<td></td>
<td>AUC₀₋₁₆₈ (pg·h/mL)</td>
<td>6796 (59.3)</td>
<td>7160 (41.8)</td>
<td>10054 (41.8)</td>
<td>8849 (58.6)</td>
<td>10054 (41.8)</td>
<td>8849 (58.6)</td>
</tr>
</tbody>
</table>

nc = not calculated; %CV is % of Coefficient of variation = 100 (standard deviation/mean)
Figure 5: Mean Serum Concentration-Time Profiles of NGMN Following Once-Daily Administration of an Oral Contraceptive for Two Cycles or Application of Norelgestromin and Ethinyl Estradiol Transdermal System for Two Cycles to the Buttock in Healthy Female Volunteers. (Oral contraceptive: Cycle 2, Days 15 to 21, Norelgestromin and Ethinyl Estradiol Transdermal System: Cycle 2, Week 3)

Table 6: Mean (%CV) for NGMN and EE Pharmacokinetic (PK) Parameters Following Application of Norelgestromin and Ethinyl Estradiol Transdermal System and Once-Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) in Healthy Female Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Norelgestromin and Ethinyl Estradiol Transdermal System</th>
<th>ORAL CONTRACEPTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGMN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1.12 (33.6)</td>
<td>2.16 (25.2)</td>
</tr>
<tr>
<td>AUC0-168 (ng·h/mL)</td>
<td>145 (36.8)</td>
<td>123 (30.2)</td>
</tr>
<tr>
<td>Css (ng/mL)</td>
<td>0.888 (36.6)</td>
<td>0.732 (30.2)</td>
</tr>
<tr>
<td>EE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>97.4 (31.6)</td>
<td>133 (27.7)</td>
</tr>
<tr>
<td>AUC0-168 (pg·h/mL)</td>
<td>12,971 (33.1)</td>
<td>8,281 (26.9)</td>
</tr>
<tr>
<td>Css (pg/mL)</td>
<td>80.0 (33.5)</td>
<td>49.3 (26.9)</td>
</tr>
</tbody>
</table>

Table 7: Mean Percent Change (%CV) in SHBG and CBG Concentrations Following Once-Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) for One Cycle and Application of Norelgestromin and Ethinyl Estradiol Transdermal System for One Cycle in Healthy Female Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Norelgestromin and Ethinyl Estradiol Transdermal System</th>
<th>ORAL CONTRACEPTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHBG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change from Day 1 to Day 22</td>
<td>334 (38.3)</td>
<td>200 (43.2)</td>
</tr>
<tr>
<td>CBG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change from Day 1 to Day 22</td>
<td>153 (40.2)</td>
<td>157 (33.4)</td>
</tr>
</tbody>
</table>

Drug Interactions

In a PK drug interaction study, oral administration of tetracycline HCl, 500 mg four times daily for 3 days prior to and 7 days during wear of norelgestromin and ethinyl estradiol transdermal system did not significantly affect the PK of NGMN or EE.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

See Warnings and Precautions (5.3, 5.12) and Use in Specific Populations (8.1).

In 3 large clinical trials lasting 12 months, in North America, Europe and South Africa, 3,330 women (ages 18 to 45) completed 22,155 cycles of norelgestromin and ethinyl estradiol transdermal system use, the pregnancy rate in women aged 18 to 35 years was 1.07 (95% confidence interval 0.60, 1.76) per 100 woman-years of norelgestromin and ethinyl estradiol transdermal system use. The racial distribution was 91% Caucasian, 4.9% Black, 1.6% Asian, and 2.4% Other.

In Table 7, percent change in concentrations (%CV) of markers of systemic estrogenic activity (Sex Hormone Binding Globulin [SHBG] and Corticosteroid Binding Globulin [CBG]) from Cycle 1 to Cycle 2 as well as the percentage of subjects with at least one patch that completely detached ranged from 2% to 6% in Norelgestromin and Ethinyl Estradiol System users compared to women taking the oral contraceptive. Percent change in CBG concentrations was similar for norelgestromin and ethinyl estradiol transdermal system and oral contraceptive users. Within each group, the absolute values for SHBG were similar for Cycle 1, Day 22 and Cycle 2, Day 22.

15 REFERENCES

Xulane® (norelgestromin and ethinyl estradiol transdermal system) is available in one strength 150 mcg/day norelgestromin and 35 mcg/day ethinyl estradiol.

**What is Xulane?**

Xulane is a birth control patch. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called norelgestromin.

Hormones from Xulane get into the blood stream and are processed by the body differently than hormones from birth control pills. You will be exposed to about 60% more estrogen if you use Xulane than if you use a typical birth control pill containing 35 micrograms of estrogen. In general, increased estrogen may increase the risk of side effects, including blood clots.

**How does Xulane work?**

Your chance of getting pregnant depends on how well you follow the directions for using Xulane. The better you follow the directions, the less chance you have of getting pregnant.

In clinical studies, 1 to 2 out of 100 women got pregnant during the first year that they used norelgestromin and ethinyl estradiol transdermal system. Xulane may not be as effective in women weighing more than 198 lbs. (90 kg). If you weigh more than 198 lbs. (90 kg), talk to your healthcare provider about which method of birth control is right for you.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.

**Patient Information**

**Xulane® [zhoou’ lan] (norelgestromin and ethinyl estradiol transdermal system)**

**No birth control**

**85 or more pregnancies per 100 women in one year**

**More pregnancies**

**10 to 20 pregnancies per 100 women in one year**

**Fewer pregnancies**

- Implants
- Intrauterine devices
- Sterilization

- Birth control pills
- Skin patch
- Vaginal rings with hormones

- Condoms
- Diaphragm

- No sex during the most fertile days of the monthly cycle
- Spermicide
- Withdrawal
Who Should Not Use Xulane?

Do not use Xulane if you:

- smoke and are over 35 years old
- have or have had blood clots in your arms, legs, eyes or lungs
- have an inherited problem that makes your blood clot more than normal
- have had a stroke
- have had a heart attack
- have certain heart valve problems or heart rhythm problems that can cause blood clots to form in the heart
- have high blood pressure that medicine cannot control
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or have any migraine headaches if you are over age 35
- have liver disease, including liver tumors, take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme “alanine aminotransferase” (ALT) in the blood.
- have unexplained vaginal bleeding
- are pregnant or think you may be pregnant. However, Xulane is not known to cause birth defects when used by accident during pregnancy.
- have had breast cancer or any cancer that is sensitive to female hormones
- Hormonal birth control methods may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy or related to previous use of hormonal birth control.

Tell your healthcare provider if you have ever had any of the above conditions.

Your healthcare provider may recommend another method of birth control.

What should I tell my healthcare provider before using Xulane?

Before you use Xulane tell your healthcare provider:

- about all your medical conditions
- if you are pregnant or think you are pregnant
- if you are scheduled for surgery. Xulane may increase your risk of blood clots after surgery. You should stop using your Xulane patch at least 4 weeks before you have surgery and not restart it until at least 2 weeks after your surgery.
- if you are scheduled for any laboratory tests. Certain blood tests may be affected by hormonal birth control methods.
- are breastfeeding or plan to breastfeed. Hormonal birth control methods that contain estrogen, like Xulane, may decrease the amount of milk you make. A small amount of hormones from the Xulane patch may pass into your breast milk. Consider another method of birth control until you are ready to stop breastfeeding.

Tell your healthcare provider about all medicines and herbal products that you take.

Some medicines and herbal products may make hormonal birth control less effective, including, but not limited to:

- certain seizure medicines (carbamazepine, felbamate, oxcarbazepine, phenytoin, rufinamide, and topiramate)
- aprepitant
- barbiturates
- bosentan
- griseofulvin
- certain combinations of HIV medicines (nelfinavir, ritonavir, ritonavir-boosted protease inhibitors)
- certain non-nucleoside reverse transcriptase inhibitors (nevirapine)
- rifampin and rifabutin
- St. John’s wort

Use another birth control method (such as a condom and spermicide or diaphragm and spermicide) when you take medicines that may make the Xulane patch less effective.

Some medicines and grapefruit juice may increase your level of the hormone ethinyl estradiol if used together, including:

- acetaminophen
- ascorbic acid
- medicines that affect how your liver breaks down other medicines (itraconazole, ketoconazole, voriconazole, and fluconazole)
- certain HIV medicines (atazanavir, indinavir)
- atorvastatin
- rosuvastatin
- etravirine

Hormonal birth control methods may interact with lamotrigine, an anti-seizure medicine used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Women on thyroid replacement therapy may need increased doses of thyroid hormone.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use Xulane?

- For detailed instructions, see the step-by-step instructions for using Xulane at the end of this Patient Information.
- Use Xulane exactly as your healthcare provider tells you to use it.
- Wear one Xulane patch at a time. Make sure you remove your old Xulane patch before applying your new Xulane patch.
- Do not skip using any Xulane patches, even if you do not have sex often.
- Xulane is applied in a 4-week cycle.
  - Apply your Xulane patch 1 time each week for 3 weeks (21 total days).
  - Apply each new Xulane patch on the same day of the week. This day will be your “Patch Change Day.” For example, if you apply your first Xulane patch on a Monday, all of your Xulane patches should be applied on a Monday.
  - Do not apply your Xulane patch during Week 4. Make sure you remove your old Xulane patch. This is your patch-free week. Your menstrual period should start during your patch-free week.
  - Begin a new 4 week cycle by applying a new Xulane patch on the day after Week 4 ends. Repeat the cycle of 3 weekly applications followed by a patch-free week.

What are the possible side effects of Xulane?

See “What is the most important information I should know about Xulane?”

Xulane may cause serious side effects, including:

- blood clots. Like pregnancy, hormonal birth control methods increase the risk of serious blood clots (see following graph), especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start using hormonal birth control and when you restart the same or different hormonal birth control after not using it for a month or more. Some studies have reported that women who use norelgestromin and ethinyl estradiol transdermal system have a higher risk of getting a blood clot. Talk with your healthcare provider about this possibility before you start using Xulane.

![Calendar](calendar.png)
provider about your risk of getting a blood clot before using Xulane or deciding which type of birth control is right for you.

It is possible to die or be permanently disabled from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are blood clots in the:

- legs (deep vein thrombosis)
- lungs (pulmonary embolus)
- eyes (loss of eyesight)
- heart (heart attack)
- brain (stroke)

To put the risk of developing a blood clot into perspective: If 10,000 women who are not pregnant and do not use hormonal birth control are followed for one year, between 1 and 5 of these women will develop a blood clot. The figure below shows the likelihood of developing a serious blood clot for women who are not pregnant and do not use hormonal birth control, for women who use hormonal birth control, for pregnant women, and for women in the first 12 weeks after delivering a baby.

Likelihood of Developing a Serious Blood Clot (Venous Thromboembolism [VTE])

*CHC = combination hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

Call your healthcare provider right away if you have:

- leg pain that will not go away
- sudden shortness of breath
- sudden blindness, partial or complete
- severe pain or pressure in your chest
- sudden, severe headache unlike your usual headaches
- weakness or numbness in an arm or leg, or trouble speaking
- yellowing of the skin or eyeballs

Other serious risks include

- liver problems including liver tumors
- gallbladder disease
- high blood pressure

The most common side effects of Xulane are:

- breast symptoms (discomfort, swelling, or pain)
- nausea
- headache
- skin irritation, redness, pain, swelling, itching or rash at the patch application site
- stomach pain
- pain during menstruation
- vaginal bleeding and menstrual disorders, such as spotting or bleeding between periods
- mood, affect and anxiety disorders

Some women have spotting or light bleeding, breast tenderness, or feel sick to their stomach during norelgestromin and ethinyl estradiol transdermal system use. If these symptoms occur, do not stop using the Xulane patch. The problem will usually go away. If it doesn’t go away, check with your health-care provider.

Less common side effects are:

- acne
- less sexual desire
- bloating or fluid retention
- blotchy darkening of your skin, especially your face
- high blood sugar, especially in women with diabetes
- high fat (cholesterol, triglycerides) levels in the blood
- depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- problems tolerating contact lenses
- weight gain

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of Xulane. For more information, ask your healthcare provider or pharmacist.

Keep Xulane and all medicines out of the reach of children.

General information about the safe and effective use of Xulane

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. Do not use Xulane for a condition for which it was not prescribed. Do not give Xulane to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about Xulane. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Xulane that is written for health professionals.

For more information, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in Xulane?

Active ingredient: norelgestromin and ethinyl estradiol

Inactive ingredient: polyethylene, polyester, polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol, dipropylene glycol, and a polyester film with a fluoropolymer coating.

Do hormonal birth control methods cause cancer?

Hormonal birth control methods do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use hormonal birth control methods because some breast cancers are sensitive to hormones.

Women who use hormonal birth control methods may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What should I know about my period when using Xulane?

When you use Xulane you may have bleeding and spotting between periods, called unplanned bleeding. Unplanned bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Unplanned bleeding occurs most often during the first few months of Xulane use, but may also occur after you have been using the
patch for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using the patch on schedule. If the unplanned bleeding or spotting is heavy or lasts for more than a few days, you should discuss this with your healthcare provider.

What if I miss my scheduled period when using Xulane?
Some women miss periods on hormonal birth control, even when they are not pregnant. However, if you go 2 or more months in a row without a period, or you miss your period after a month where you did not use all of your patches correctly, or you have symptoms associated with pregnancy, such as morning sickness or unusual breast tenderness, call your healthcare provider because you may be pregnant. Stop taking Xulane if you are pregnant.

What if I want to become pregnant?
You may stop using Xulane whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop using the patch.

Instructions for Use
Xulane is for skin use only.
Do not cut, damage, or alter the Xulane patch in any way.

How to start using your Xulane patch:

- If you are not currently using hormonal birth control, you have 2 ways to begin using your Xulane patch. Choose the way that is best for you:
  - **First day start:** Apply your first Xulane patch during the first 24 hours of your menstrual period.
  - **Sunday start:** Apply your first Xulane patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first Xulane patch that day, and no back-up birth control is needed.

- If you are changing from the pill or vaginal contraceptive ring to the Xulane patch:
  - Complete your current pill cycle or vaginal ring cycle. Apply your first Xulane patch on the day you would normally start your next pill or insert your next vaginal ring.
  - If you do not get your period within 1 week after taking your last active pill or removing your last vaginal ring, check with your healthcare provider to make sure you are not pregnant. You may still go ahead and start Xulane for contraception.
  - If you apply your Xulane patch more than 1 week after taking your last active pill or removing your last vaginal ring, use a non-hormonal contraceptive method with the Xulane patch for the first 7 days of patch use.

- If you are starting Xulane after childbirth:
  - If you are not breastfeeding, wait 4 weeks before using Xulane and use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If you have had sex since your baby was born, wait for your first period, or see your healthcare provider to make sure you are not pregnant before starting Xulane.

- If you are starting Xulane after a miscarriage or abortion:
  - You may start Xulane immediately after a miscarriage or abortion that occurs in the first 12 weeks (first trimester) of pregnancy. You do not need to use another contraceptive method.

  - If you do not start Xulane within 5 days after a first trimester miscarriage or abortion, use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, while you wait for your period to start. You have 2 ways to begin using your Xulane patch. Choose the way that is best for you:
    - **First day start:** Apply your first Xulane patch during the first 24 hours of your menstrual period.
    - **Sunday start:** Apply your first Xulane patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first Xulane patch that day, and no back-up birth control is needed.

  - If you are starting Xulane after a miscarriage or abortion that occurs after the first 12 weeks of pregnancy (second trimester), wait 4 weeks before using Xulane and use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If you have had sex since your miscarriage or abortion, wait for your first period, or see your healthcare provider to make sure you are not pregnant before starting Xulane.

Figure B is a picture of the Xulane patch.

Step 1. Choose a place on your body for your Xulane patch:

- The Xulane patch may be placed on your upper outer arm, abdomen, buttock or back in a place where it will not be rubbed by tight clothing. Avoid the waistline because clothing and belts may cause your patch to be rubbed off.
- **Do not** apply the patch to your breasts.
- Apply the Xulane patch only to skin that is clean, dry, and free of any powder, make-up, cream, oil, or lotion.
- Do not apply the Xulane patch to cut or irritated skin, or in the same location as the previous Xulane patch.

**Step 2: Apply your Xulane patch**

<table>
<thead>
<tr>
<th>Image 51x635 to 128x711</th>
<th>• Tear open the pouch at the top edge and one side edge. Peel open the foil pouch. Gently remove the contents of the foil pouch and discard the additional pieces of film above and below the Xulane patch.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image 51x546 to 129x615</td>
<td>• Peel away half of the clear plastic. Avoid touching the sticky surface with your fingers.</td>
</tr>
<tr>
<td>Image 52x457 to 129x524</td>
<td>• Apply the sticky side of the Xulane patch to clean, dry skin. Remove the other half of the clear plastic and apply the entire patch to your skin.</td>
</tr>
<tr>
<td>Image 53x364 to 129x431</td>
<td>• Press firmly on the Xulane patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to your skin. Run your fingers over the entire surface area to smooth out any &quot;wrinkles&quot; around the outer edges of the Xulane patch. Check your Xulane patch every day to make sure all edges are sticking correctly.</td>
</tr>
</tbody>
</table>

**Step 3: Throwing away your Xulane patch**

- To throw away the Xulane patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place the container in the trash.

- Used Xulane patches should not be flushed in the toilet.

**Important notes:**

- Your Xulane patch must stick securely to your skin to work properly.
- Do not try to reapply a Xulane patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it. Do not tape or wrap the patch to your skin or reapply a patch that is partially adhered to clothing.

- If your Xulane patch edge lifts up:
  - Press down firmly on the patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to your skin. Run your fingers over the entire surface area to smooth out any "wrinkles" around the edges of the Xulane patch.
  - If your Xulane patch does not stick completely, remove it and apply a new Xulane patch.
  - Do not tape or wrap the Xulane patch to your skin or reapply a Xulane patch that is partially stuck to clothing.

- If your Xulane patch has been off or partially off:
  - For less than 1 Day, try to reapply it. If the Xulane patch does not stick completely, apply a new Xulane patch immediately. No back-up contraception is needed and your "Patch Change Day" will stay the same.

- For more than 1 Day or if you are not sure for how long, you could become pregnant. To reduce this chance, apply a new Xulane patch and start a new 4 week cycle. You will now have a new “Patch Change Day.” Use a non-hormonal back-up contraception method such as a condom and spermicide or diaphragm and spermicide for the first week of your new 4 week Xulane cycle.

- If you want to move your “Patch Change Day” to a different day of the week, finish your current cycle. Remove your third Xulane patch on the correct day.
  - **During week 4**, the “Patch Free Week” (Day 22 through Day 28), you may choose an earlier “Patch Change Day” by applying a new patch on the day you prefer. You now have a new Day 1 and a new “Patch Change Day.”

- If your Xulane patch becomes uncomfortable or your application site is red, painful or swollen, change your Xulane patch. Remove your Xulane patch and apply a new patch to a new location until your next “Patch Change Day.”

- If you forget to change or remove your Xulane patch:
  - **At the start of any patch cycle (Week 1, Day 1):**
    - You could become pregnant. You must use a back-up contraception method for 7 days. Apply the first Xulane patch of your new cycle as soon as you remember. You now have a new “Patch Change Day” and a new Day 1.
  - **In the middle of your patch cycle (Week 2 or Week 3):**
    - If you forget to change your Xulane patch for 1 or 2 days, apply a new Xulane patch as soon as you remember. Apply your next patch on your normal “Patch Change Day.” No back-up contraception method is needed.
    - If you forget to change your Xulane patch for more than 2 days, you could become pregnant. Start a new 4 week cycle as soon as you remember by putting on a new Xulane patch. You now have a different “Patch Change Day” and a new Day 1. You must use a back-up contraception method for the first 7 days of your new cycle.
  - **At the end of your patch cycle (Week 4):**
    - If you forget to remove your Xulane patch, take it off as soon as you remember. Start your next cycle on your normal “Patch Change Day,” the day after Day 28. No back-up contraception method is needed.

- If you forget to apply your Xulane patch at the start of your next patch cycle, you could become pregnant. Apply the first Xulane patch of your new cycle as soon as you remember. You now have a new “Patch Change Day” and a new Day 1. Use a non-hormonal back-up contraception method such as a condom and spermicide or diaphragm and spermicide for the first 7 days of your new 4 week Xulane cycle.

- If you have trouble remembering to change your Xulane patch, talk to your healthcare provider about how to make patch changing easier or about using another method of contraception.

- If you are not sure how to use your Xulane patch:
  - Use a back-up contraception method such as a condom and spermicide or diaphragm and spermicide anytime you have sex. Make sure to have one of these non-hormonal contraception methods ready at all times.
  - Talk to your healthcare provider for instructions on using your Xulane patch.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

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